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Challenges in parenteral formulation development studies and an evaluation from Quality by Design(QbD) point of view

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Parenterals & Injectables, Chicago/USA
17.08.2015

Sanovel

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  - Regulatory Definitions
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  - Why are we talking about QbD?
  - QbD terminology
  - Traditional vs QbD Aproach
  - QbD Generic Case study
- Conclusion

Regulatory Definitions

...intended for injection through the skin or other external boundary tissue, rather than through the alimentary canal, so that active substances they contain are administered, using gravity or force, directly into a blood vessel, organ, tissue or lesion*.

...are sterile preparations intended for administration by injection, infusion or implantation into the human or animal body**.

**USP, Monographs: Dosage forms: General monographs: Parenteral preparations*
***European Pharmacopoeia, Parenteral*

Other definitions…

- Medicine taken into the body or administered in a manner other than through the digestive tract, as by intravenous or intramuscular injection.
- Most effective and common form of delivery for active drug substances with metabolic bio-availabilities drug for which the bio-availability in limited by high first pass metabolism effect of other physicochemical limitation and for drugs with a narrow therapeutic index.

**Monographs: Dosage forms: General monographs: Parenteral preparations*

Advantages and Disadvantages of Parenteral Drugs and Administration

Advantages*:

- Useful for drugs that require **a rapid onset of action**
- Useful for patients who can **not take drugs orally**
- Suitable for the drugs which **are not administered by oral route**
- Useful for **emergency situations**
- Useful for **unconscious or vomiting patients**
- Duration of action can be **prolonged by modifying formulation**
- Suitable for the drugs which are **inactivated in GIT or CI(GI fluid)**

**Encyclopedia of Pharmaceutical Technology, Vol 1, Dosage Forms: Parenterals*

Advantages and Disadvantages of Parenteral Drugs and Administration

Disadvantages*:

- More **expensive** and **costly to produce**
- Once injected can **not be** controlled(**retreat**)
- Injections **may cause pain** at the site of injection
- Potential for tissue damage upon injection
- Require **specialized equipment, devices and techniques** to prepare and administer drugs
- If given by wrong route, **difficult to control adverse effect**
- Difficult to save patient if overdose
- Sensitivity or allergic reaction at the site of injection
- Requires **strict control of sterility&non pyrogenicity** than other formulation

**Encyclopedia of Pharmaceutical Technology, Vol 1, Dosage Forms: Parenterals*

Why parenteral?

Benefit	Oral	Injectable
Rapid onset of action		✓
Less expensive	✓	
Administrable to nonresponsive patients		✓
Patient convenience and comfort	✓	
Administrable directly to site of action		✓
Retrievable, if necessary	✓	
Better absorption		✓

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Formulation of parenteral products

Volume:

- **Small volume parenterals(SVP):** 100 mL or less and can be provided as single-or multidose product.
- **Large volume parenterals(LVP):** more than 100 mL, single-dose injection.

Clinical use:

- Imigation solution
- Dialysis solution
- Diagnostic agent
- Ophthalmic products

Physical use:

- Sterile solutions
- Sterile suspensions
- Sterile emulsions
- Sterile solid

Formulation of parenteral products

Type of packaging

- Single dose preparations: to permit the withdrawal and administration of the nominal dose using a normal technique.
- Infusion solution
- Multiple dose preparations:contain a suitable **antimicrobial preservative** at an appraprate concentration except when the preparation itself has adequate animicrobial properties, and in order to minimize the risk of contamination multidose preparation should normally **not exceed 30 mL**.

Formulation of parenteral products

Injection: Liquid preparations that are drug substances or **solutions** thereof*(ready for injection)*

For Injection: **Dry** solids(**powders**) that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for Injections*(soluble products ready to be combined with a solvent just prior to use)*

Injectable Emulsion:Liquid preparations of drug substances dissolved or dispersed in a suitable emulsion vehicles and added substances medium

**USP, Monographs: Dosage forms: General monographs: Parenteral preparations*

Formulation of parenteral products

Injectable Suspension:Liquid preparations of solids suspended in a suitable liquid medium.

For Injectable Suspension: Dry solids(**powders**) that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Injectable Suspensions.

**USP, Monographs: Dosage forms: General monographs: Parenteral preparations*

Formulation of parenteral products: Solutions

Most injectable products are aqueous solutions.

Dissolving drugs and excipients

↓

Adjusting the pH

↓

Sterile filtering

↓

Aseptic filling

↓

Autoclaving

Sterile filtration with subsequent aseptic filling is common because of the heat sensitivity of many drugs.

Formulation of parenteral products: Dry Powder

Many APIs are **unstable-either physically or chemically-** in an aqueous medium to allow formulation as a solution, suspension or emulsions. Instead, the drug is formulated as a dry powder that is **reconstituted by addition of water before administration**.

Advantages of Freeze drying:

- Avoid damage to **heat-sensitive drugs**
- High specific surface are facilitating complete rehydration
- Improvement in filling accuracy
- Product is stored in dry state-few stability problems

Disadvantages of Freeze drying:

- **Protective agents** needed
- Stability changing, crystalline/amorphous
- **High-cost** and complicated

Formulation of parenteral products

Emulsions are rarely used as parenteral products.

- Excellent **stability** requirement
- **Particle size**<1um, homodispersity
- Very limited selection of stabilizers&emulsifiers

Suspensions: It is very difficult to formulate and produce.

Components
Active ingredients
Aqueous vehicle
Surfactant for wetting
Preservatives
Buffers

Unique characteristics of parenterals

- ✓All products must be **sterile**.
- ✓All products must be **free from pyrogenic** (endotoxin) contamination.
- ✓Injectable solutions must be free from visible **particulate matter**. This includes reconstituted sterile powders.
- ✓Products should be isotonic, although strictness of isotonicity depends on the route of administration.
- ✓All products must be stable, not only chemically and physically like all other dosage forms, but also **'stable' microbiologically** *(i.e., sterility, freedom from pyrogenic and visible particulate contamination must be maintained throughout the shelf life of the product).*
- ✓Products must be **compatible**, if applicable, with IV diluents, delivery systems, and other drug products co-administered.
- ✓Specific and **high quality packaging** is needed.

Sample chapter from Remington: Essentials of Pharmaceutics, Parenteral Preparations, Michael J. Akers.

Formulations: Choosing right excipients

- The basic approaches to addition of excipients is kept to minimum.
- All excipients must meet compendial standarts.
- There must be no incompatibility between any of the components of the dosage form.
- They do not adversely affect the stability, bioavailability, safety or efficacy of the active ingredient(s) or cause toxicity or local irritation.

Formulations: Choosing right excipients

- Increase and maintain drug solubility*(**complexing agents**(b-cyclodextrins) and **surface active agents**(polysorbate, lecithin)*
- Provide patient comfort by reducing pain and tissue irritation
- Make a solution isotonic*(**tonicity agents**: sodium chloride, dextrose, and glycerin) or near physiological pH(**adjusting agents**)*
- Enhance the chemical stability of a solution*(**antioxidants:** Ascorbic acid isomers, sulfurous acid salts, thiol derivatives) inert gases, chelating agents, and **buffers:** acetic acid–acetate, citric acid–citrate)*
- Enhance the chemical and physical stability of a freeze-dried product*(**cryoprotectants** and **lyoprotectants**)*

Formulations: Choosing right excipients

- Protect a preparation against the growth of microorganisms *(**Antimicrobial preservatives:*** methylparaben, propylparaben, benzyl alcohol, benzalkonium chloride*)*

- Sustaining and/or controlling drug release*(**polymers**)*

- Maintaining the drug in a suspension dosage form *(**suspending agents**, usually polymers and surface active agents)*

- Establishing emulsified dosage forms *(**emulsifying agents**, usually amphiphilic polymers and surface active agents), and preparation of liposomes (hydrated phospholipids)*

  - *An **inert gas** (such as nitrogen) can also be used to enhance drug stability whereby the air in the container is replaced by this gas.*

Formulation:Basic Approaches to Develop Parenteral Drug Product

- Obtain physical properties of active drug substance *(Structure, molecular weight, "Practical" solubility in water at room temperature, Effect of pH on solubility, Solubility in certain other solvents, Unusual solubility properties, Hygroscopicity)*

- Obtain chemical properties of active drug substance*(Must have a 'validatable' analytical method for potency and purity, Time for 10% degradation at room temperature in aqueous solution in the pH range of anticipated use, Time for 10% degradation at 5°C, pH stability profile, Sensitivity to oxygen, Sensitivity to light, Major routes of degradation and degradation products, polymorphic conversion)*

Formulation:Basic Approaches to Develop Parenteral Drug Product

- Initial formulation approaches
  - Know how drug product will be used in the clinic*(Single dose vs multiple dose; If multiple dose, will preservative agent be part of drug solution/powder or part of diluent?)*
  - Shelf life goals
  - Combination with other products, diluents*(Chemical Stability in Infusion Solutions)*
  - From knowledge of solubility and stability properties*(formulate drug with components and solution properties known to be successful at dealing with these issues, then perform accelerated stability studies)*
  - High temperature storage
  - Light and/or oxygen exposure
  - For powders, expose to high humidities

Formulation:Basic Approaches to Develop Parenteral Drug Product

- Finalize formulation*(Need for tonicity adjusting agent, Need for antimicrobial preservative, Osmolality)*
- May need to perform several short-term stability studies*(as excipient types and combinations are eliminated)*
- Selection of primary container and closure*(Be aware of potential for tubing glass to be subject to glass delamination (glass lamellae); work with glass supplier to select type of glass; Most rubber closure formulations are coated rubber to minimize leachables and do not require siliconization)*
- Design and implement an initial manufacturing method of the product
- Approach to obtain sterile product*(Terminal sterilization, Sterile filtration(Bacterial challenging test for filter validation, Compatibility study with filters) and aseptic processing)*

Formulation:Methods of Sterilization

Steam(autoclave): Steam sterilization is conducted in an autoclave and employs steam under pressure.

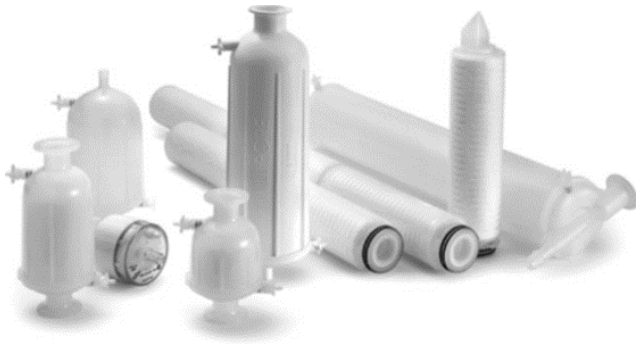
The usual temperature and the approximate length of time required is 121°C for 15 to 30 minutes, depending on the penetration time of moist heat into the load.

Dry heat: The transfer of energy from dry air to the object that is sterilized. The transfer occurs through conduction, convection and radiation, higher temperature and longer time are required*(250°C for two hours).*

The effectiveness of any sterilization technique must be proved(validated).

Formulation:Methods of Sterilization

Filtration: Sterilization by filtration depends on the physical removal of microorganisms by adsorption on the filter medium or by a sieving mechanism, for heat-sensitive solutions, membrane filters(0.22 µm).



Membrane filters are used exclusively for parenteral solutions, due to their particle-retention effectiveness, non-shedding property, non-reactivity, and disposable characteristics.

The effectiveness of any sterilization technique must be proved(validated).

Formulation:Methods of Sterilization

Filtration: The most common membranes are composed of Cellulose esters, Nylon, Polysulfone, Polycarbonate, PVDF, Polyethersulfone(PES) or Polytetrafluoroethylene(Teflon).

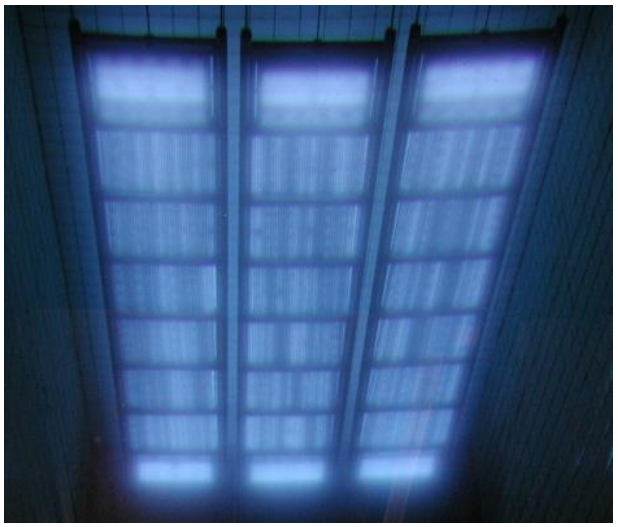
The **integrity of the filters** has to be proven.

If the drug formulation content benzyl alcohol, it is recommended to use nylon filter instead of PES filter due to the incompatibility issue.

The effectiveness of any sterilization technique must be proved(validated).

Formulation:Methods of Sterilization

Ionizing radiation: High-energy photons are emitted from an isotope source (Cobalt 60) producing ionization throughout a product. It can be applied under safe, well-defined, and controlled operating parameters, and is not a heat- or moisture generating process.



Most importantly, there is no residual radioactivity after irradiation ***(Gamma Radiation)***.

The effectiveness of any sterilization technique must be proved(validated).

Containers and Closures: Types of packaging

"*A container closure system refers to the **sum of packaging components that together contain and protect the dosage form**. This includes **primary packaging components and secondary packaging components**, if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system*." FDA 1999

*"The **primary packaging components** (e.g. bottles, vials, closures, blisters) are in **direct physical contact with the product**, whereas the **secondary components are not** (e.g. aluminium caps, cardboard boxes)." WHO guideline "Guidelines on packaging for pharmaceutical products, Annex 9"*

Selecting types of packaging is a critical point because packaging components are the major source of particulate matter; pyrogen and stability problems.

Containers and Closures: Types of packaging

Packaging must be **a barrier to the external environment and maintain the sterility of its contents** and also serve to shield the drug product from oxidation, light degradation and moisture permeation.

Factors of selecting glass packaging on the products :

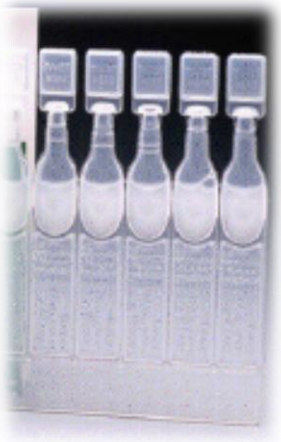
- Types of the product
- pH of aqueous solution
- Constituents of aqueous solution
- Sterilization technique*(as heat sterilization cause change in color stability, pH...)*

USP Classification of Glass

Type-I, a borosilicate glass
Type-II, a soda-lime treated glass
Type-III, a soda-lime glass
NP, a soda –lime glass not suitable for containers for parenterals

Containers and Closures: Types of packaging

Plastic: One of the disadvantages of plastics is substance can be leakage from plastic into solution*(polymers as polyethylene-polypropylene)*



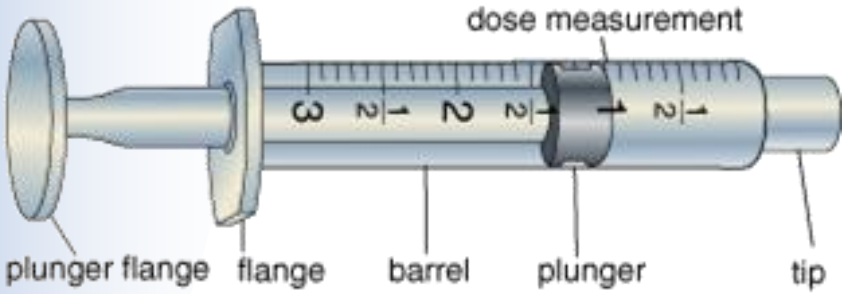
Rubber: usually used as closures, sufficiently elastic to allow the puncture to reseal when the needle is withdrawn and protect the contents from airborne contamination for multidose*(bromobutyl, chlorobutyl, butyl)*

Containers and Closures: Types of packaging

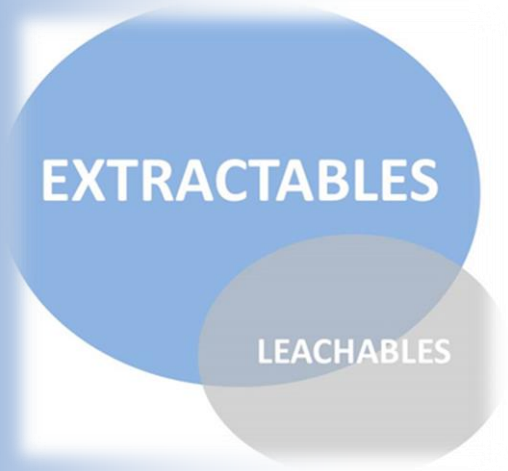
Pre-filled syringes may make easy administration in an generally emergency situation.

Syringes are used for IV push and in the preparation of infusions, are made of glass or plastic.

- **Glass syringes** are more expensive*(use limited to medications that are absorbed by plastic)*
- **Plastic syringes** are less expensive*(are disposable, come from the manufacturer sterile)*



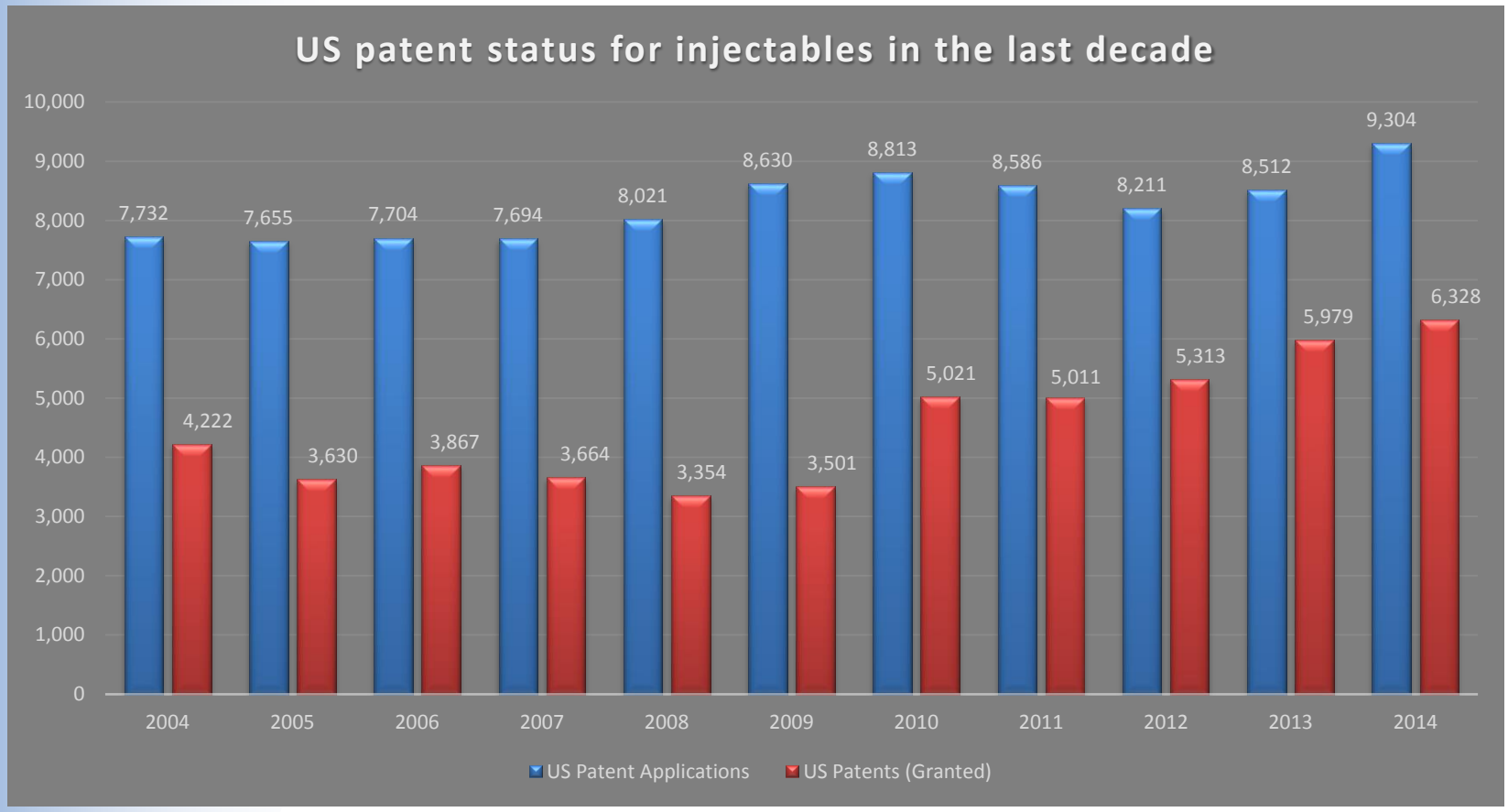
Containers and Closures:Leachables&Extractables



If the product is sensitive to the presence of ions, such as boron, sodium, potassium, calcium, iron and magnesium, great care must be taken in selecting the appropriate glass container, as these ions may leach from the glass container and interact with the product, reducing chemical stability, inducing formation of particulate or altering pH of solution.

Major extractables are silicon and sodium; minor extractables include potassium, barium, calcium and aluminum.

Intellectual Properties for Injectables



Keyword: Title/Abstract/Claim: injectable OR parenteral* OR infusion* OR injection**

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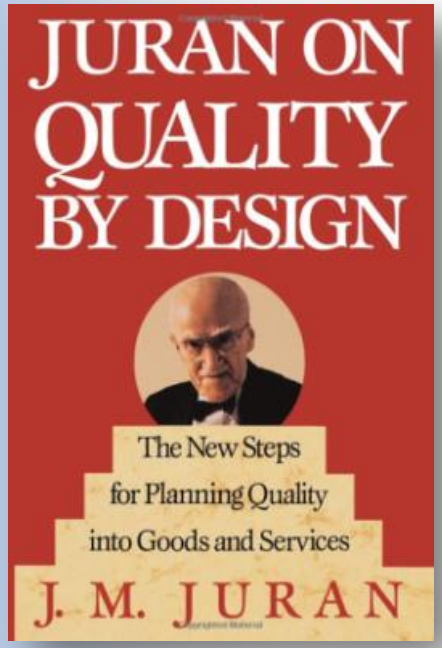
Evaulation from Quality by Design point of view

Quality by Design (QbD) is a concept first outlined by Juran.



‘quality should be designed into a product and that most quality crises and problems relate to the way in which a product was designed in the first place’

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management*.

**Pharmaceutical Development-ICH Q8*

The goals of QbD

- To achieve **meaningful product quality specifications** that are based on clinical performance
- To increase **process capability** and reduce **product variability and defects** that often leads to product defects, rejections and recalls by enhancing product and process design, understanding and control
- To increase **product development and manufacturing efficiencies**
- To enhance **root cause analysis** and **post-approval change management**
- Achieving this objective requires **robustly designed product and process**

Industry applications

ICH Q8, Q9, Q10, Q11 are designed as separate but linked in a series of documents exploring pharmaceutical products lifecycle/

- ICH Q8 Pharmaceutical Development
- ICH Q9 Quality Risk Management
- ICH Q10 Pharmaceutical Quality System
- ICH Q11 Development and Manufacture of Drug Substances

ICH guidelines are desribed the QbD principles and concepts to development and manufacture of drug substance.

These documents provide high level directions with respect to the scope and definition of QbD as it applies to the pharmaceutical industry.

ICH harmonisation for better health

Industry applications

FDA encourages risk-based approaches and the adoption of QbD principles in drug product development, manufacturing and regulation.

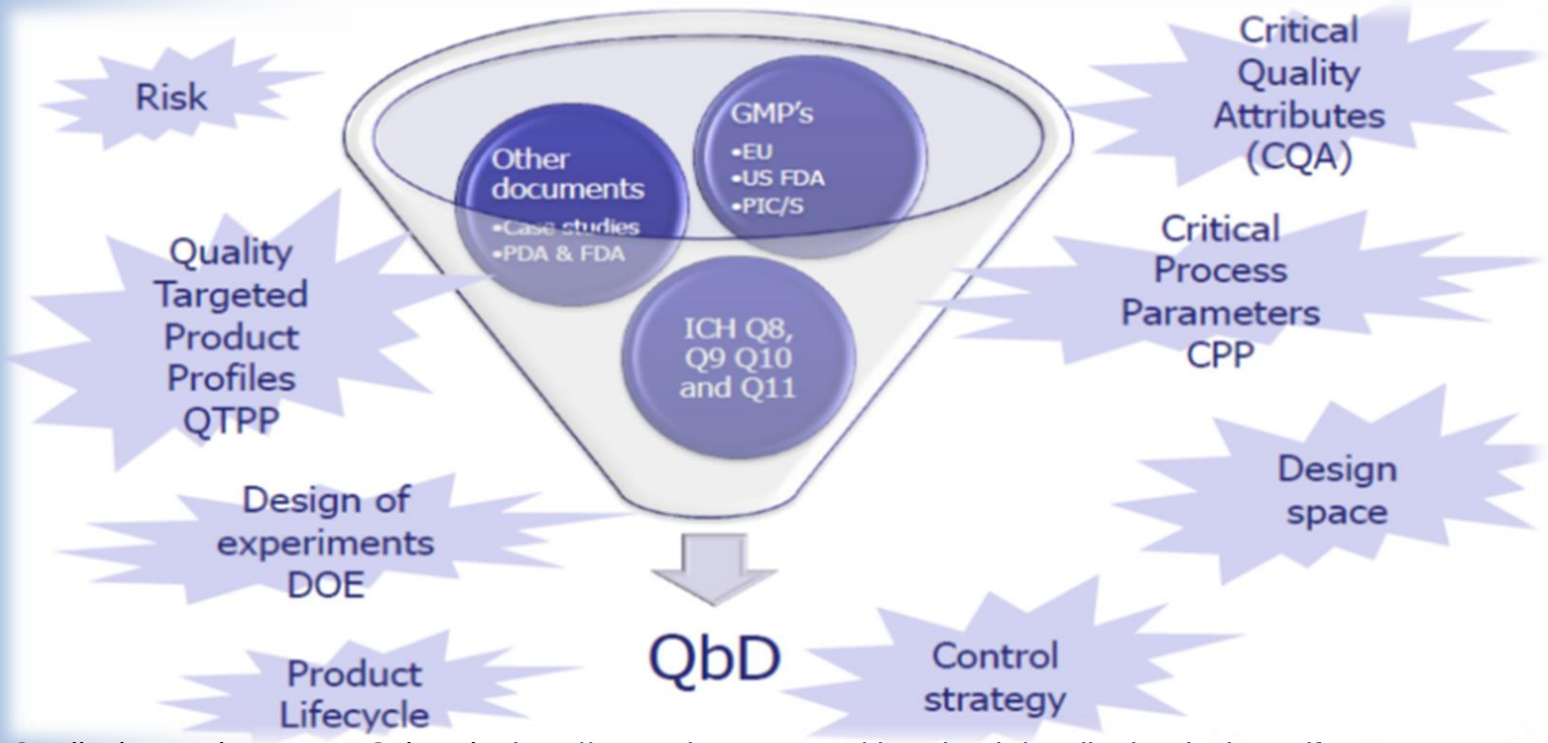
Applying Quality by Design to Vaccines CMC Vaccines Working Group, *May 2012*
Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms, *April 2012*
Quality by Design for ANDAs: An example for Modified Release Dosage Forms, *Dec 2011*

Pharmaceutical Quality= $_f$(drug substance, excipients, manufacturing, packaging)

Quality can not be tested into products but should be built in by design.

Why are we talking about QbD?

QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.



Quality by Design Trevor Schoerie, http://www.pharmout.net/downloads/quality-by-design.pdf

QbD terminology: Quality Target Product Profile

TPP/QTPP: a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product, *ICH Q8*

- Intended use in a clinical setting, **route of administration**, dosage form, and delivery system(s)
- **Dosage strength**(s)
- **Container closure system**
- **Drug product quality criteria** (e.g., sterility, purity, stability, and drug release) appropriate for the intended marketed product

QTPP is an essential element of a QbD approach. The lack of a well-defined QTPP has resulted in wasted time and valuable resources.

QbD terminology:Critical Quality Attribute

"A **CQA** is a physical, chemical, biological or microbiological property or characteristic of an output material including finished drug product that should be within an appropriate limit, range or distribution to ensure the desired product quality." *ICH Q8*

Chemical attributes: Assay, content uniformity, degradation products, residual solvents, drug release or dissolution, moisture content, microbial limits, stability...

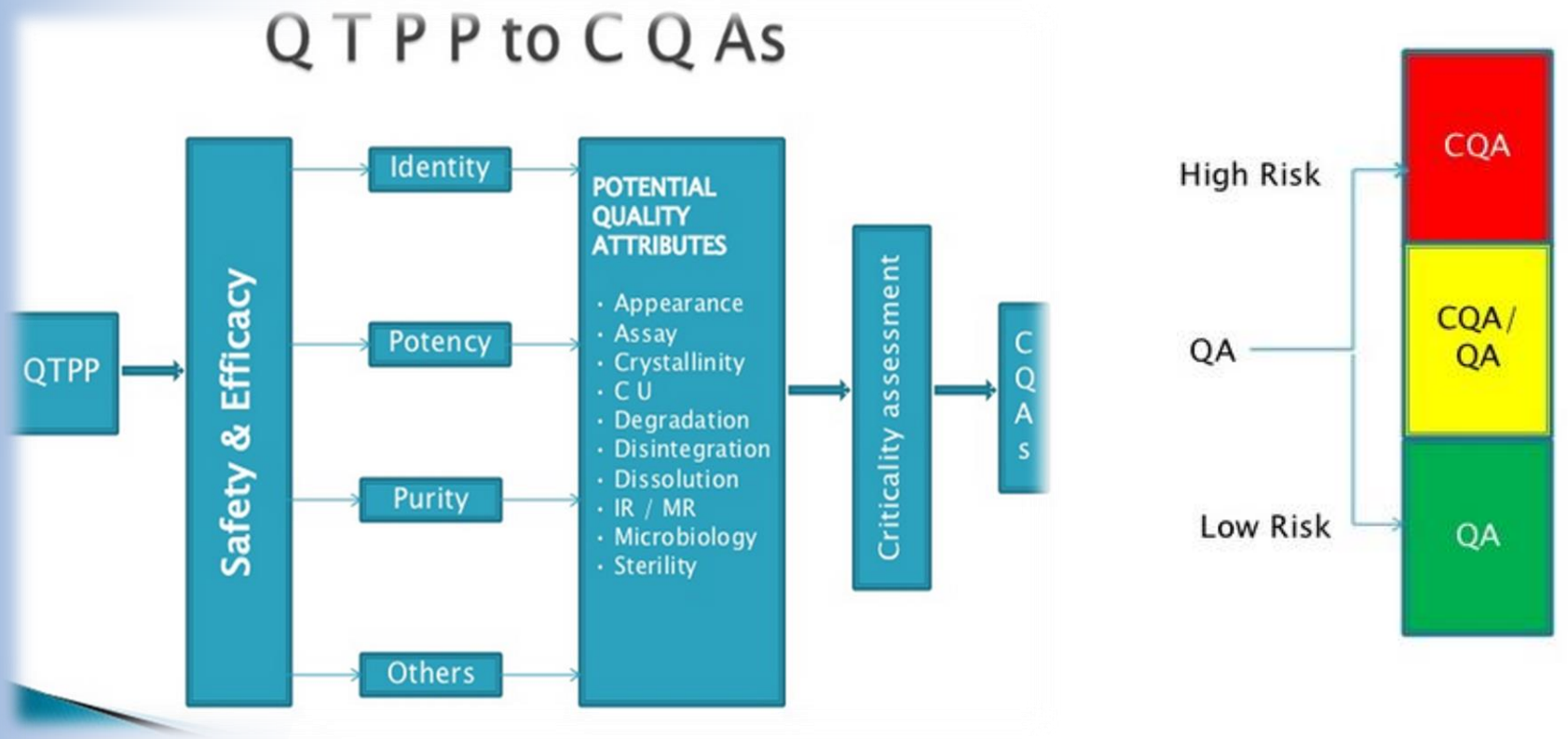
Physical attributes: Color, shape, size, odor, score configuration, friability, particle size distribution and particle morphology, polymorphism, identity, aqueous solubility as a function of pH, hygroscopicity, melting point...

Quality attributes must be controlled within pre-defined limits.

QTPPs are patient and clinical outcome metrics; CQAs are drug product/substance quality metrics.

When is a Quality Attribute a CQA?

Drug product CQAs derived from the QTPP and/or prior knowledge.



CQAs are used to guide the product and process development.

QbD terminology:Critical Material Attribute

"A **CMA** is a physical, chemical, biological or microbiological property or characteristic of an input material that should be within an appropriate limit, range or distribution to ensure the desired quality of that drug substance, excipient or in-process material.*

Pharmaceutical unit operation

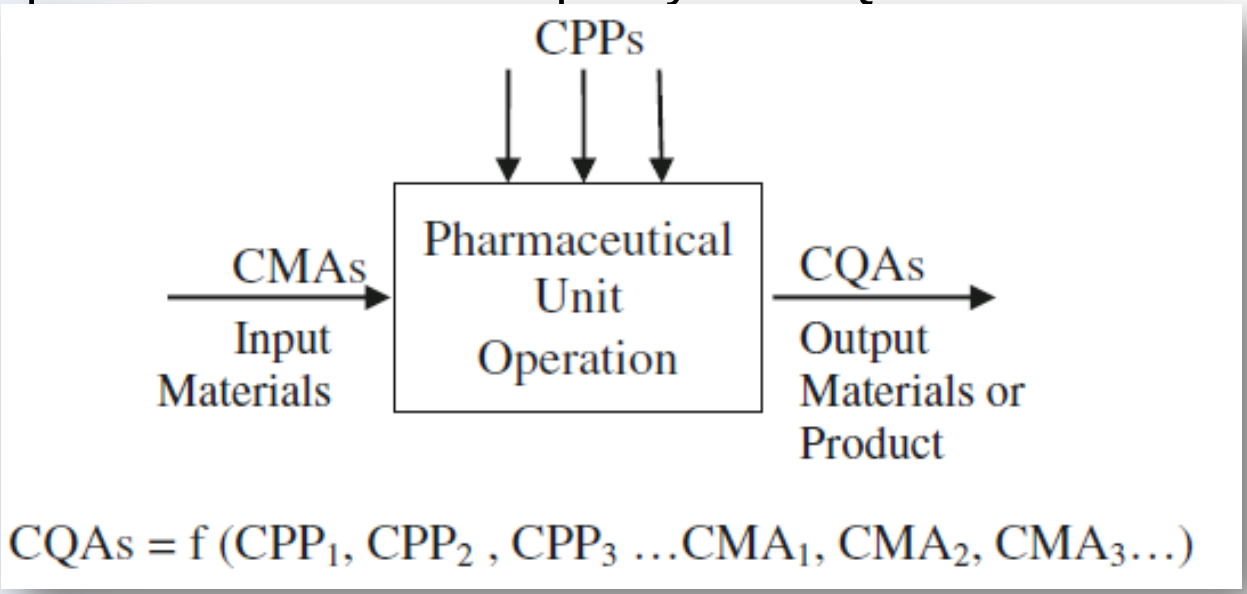
Input material attributes	Process parameters	Quality attributes
	Blending/mixing	
• Particle size • Particle size distribution • Fines/oversize • Particle shape • Bulk/tapped/true density • Cohesive/adhesive properties • Electrostatic properties • Moisture content	• Type and geometry of mixer • Mixer load level • Order of addition • Number of revolutions (time and speed) • Agitating bar (on/off pattern) • Discharge method • Holding time • Environment temperature and RH	• Blend uniformity • Potency • Particle size • Particle size distribution • Bulk/tapped/true density • Moisture content • Flow properties • Cohesive/adhesive properties • Powder segregation • Electrostatic properties

*CQAs are for **output materials** including product intermediates and finished drug product while CMAs are for **input materials** including drug substance and excipients.*

**Understanding Pharmaceutical Quality by Design, The AAPS Journal, Vol. 16, No. 4, July 2014*

QbD terminology: Critical Process Parameter

"**CPP** is a process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality." *ICH Q8*



CPPs have a direct impact on the CQAs, can be measured and controlled and a process parameter that must be controlled within pre-defined limits assurance the product meets its pre-defined quality attributes.

QbD terminology: CPPs and CQAs for Injectables

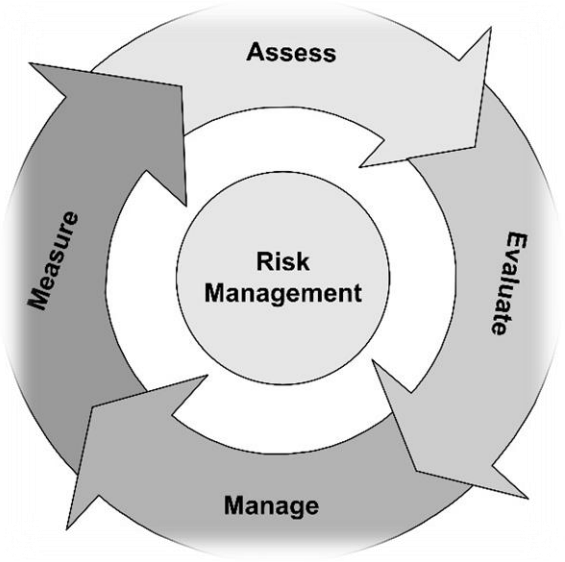
Process variable	CPP	CQA
Mixing	Capacity of Unit	Potency Appearance pH Viscosity
	Fill volume	
	Temperature of liquid and time	
	Mixing time	
	Mixing speed	
Filtration	Filter type and size	Potency Appearance pH Impurity Microbiological tests
	Filtration speed	
	Filtration time	
	Pump type	
Filling&Sealing	Filling speed	Potency Appearance pH Impurity Microbiological tests Weighing controls
	Filling time	
	Pump type	

QbD terminology:Quality Risk Management

QRM; is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product.

Quality risk management indicates that “the manufacturing and use of a drug product, including its components, necessarily entail some degree of risk*” ICH Q9*

“Combination of the probability of occurrence of harm and the severity of that harm” *ICH Q9*

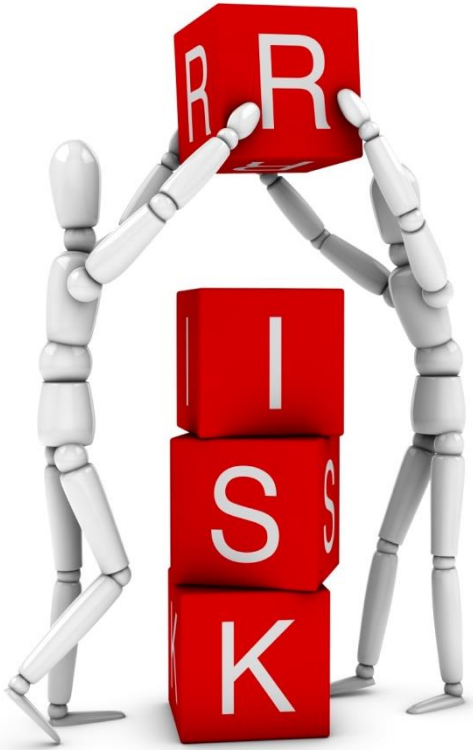


QbD terminology:Quality Risk Management

QRM system should be ensure the evaluation of the risk to quality is **based on scientific knowledge**, **experience** with the process and ultimately links to the protection of the patient.

Risk assessment is used to identify and link CMAs and CPPs to the drug product CQAs.

The purpose of risk assessment prior to development studies is to identify potentially high-risk formulation and process variables that could impact the quality of the drug product.



The outcome of the risk assessment is to identify the variables to be experimentally investigated.

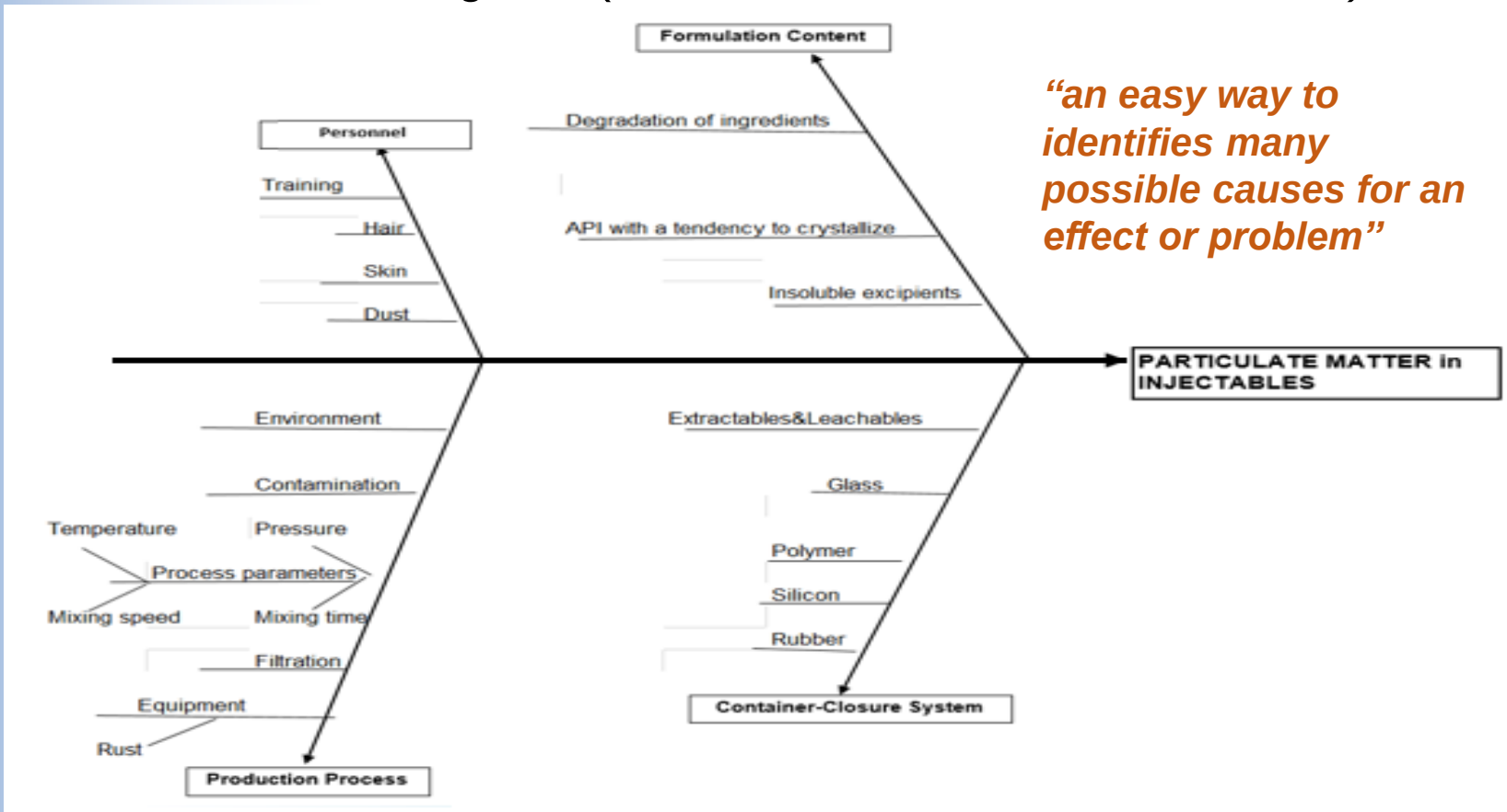
Yu et al. Understanding Pharmaceutical Quality by Design, The AAPS Journal (March 2014)

QbD terminology:Quality Risk Management

Risk Asessment Tools
Process mapping
Cause and Effect Diagrams(Ishikawa charts or fishbone charts)
Preliminary Hazard Analysis(PHA)
Hazard Analyses of Critical control Points(HACCP)
Hazard Operability Analyses(HAZOP)
Fault Tree Analyses(FTA)
Failure Mode Effects Analyses(FMEA)
Failure Mode, Effects and Criticality Analyses(FMECA)
Risk Ranking and Filtering
Informal Risk Management
Taguchi, variation risk management method

QbD terminology:Quality Risk Management

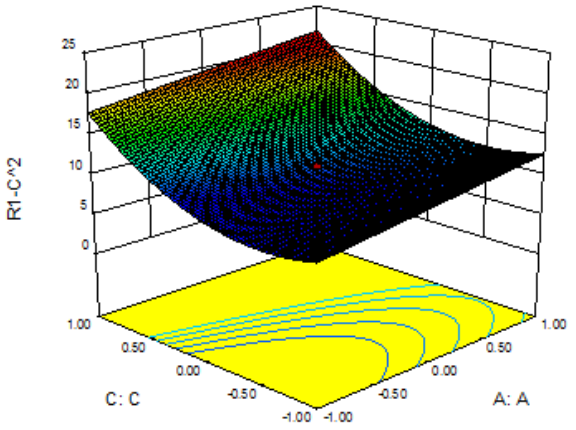
Cause and Effect Diagrams(*Ishikawa charts* or *fishbone charts)*



"an easy way to identifies many possible causes for an effect or problem"

QbD terminology: Design Space

"Multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality*" ICH Q8 (R2)*

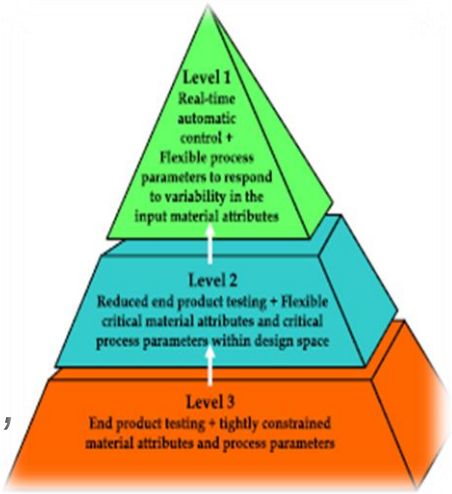


QbD does not equal design of experiments (DoE), but the latter could be an important component of QbD. It is optional and not required.

Working within the design space is not considered as a change.

QbD terminology: Control Strategy

- ✓ Control of **input material** attributes *(e.g., drug substance, excipient, in process material, and primary packaging material) based on an understanding of their impact on processability or product quality & product specification(s)*
- ✓ Controls for **unit operations** that have an impact on downstream processing or product quality *(e.g., the impact of drying on degradation and particle size distribution of the granulate on dissolution)*
- ✓ **In-process or real-time release testing** in lieu of end-product testing *(e.g., measurement and control of CQAs during processing)*
- ✓ A **monitoring program** *(e.g., full product testing at regular intervals)* for verifying multivariate prediction models



Control strategy is a planned set of controls that ensures process performance and product quality.

QbD terminology: Process Analytical Technology

The application of PAT may be part of the control strategy.

PAT can provide continuous monitoring of CPPs, CMAs or CQAs to make go/no go decisions and to demonstrate that the process is maintained in the design space. In-process testing, CMAs or CQAs can also be measured online or inline with PAT.

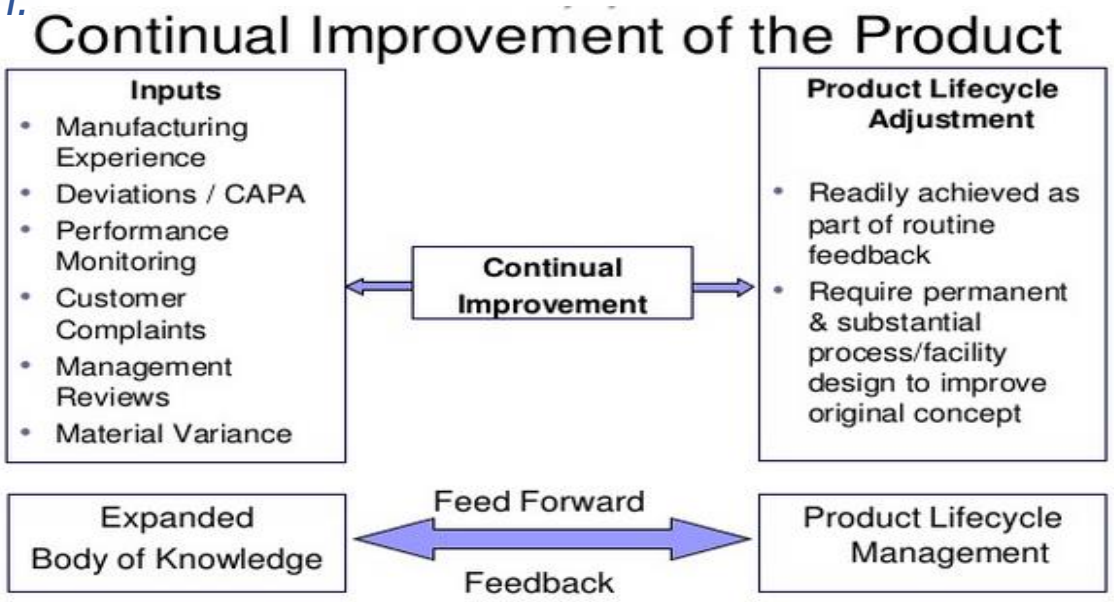
PAT can help mitigate the risk by increasing the level of control.

Product and process understanding is a key element of QbD.

QbD terminology: Continual Improvement

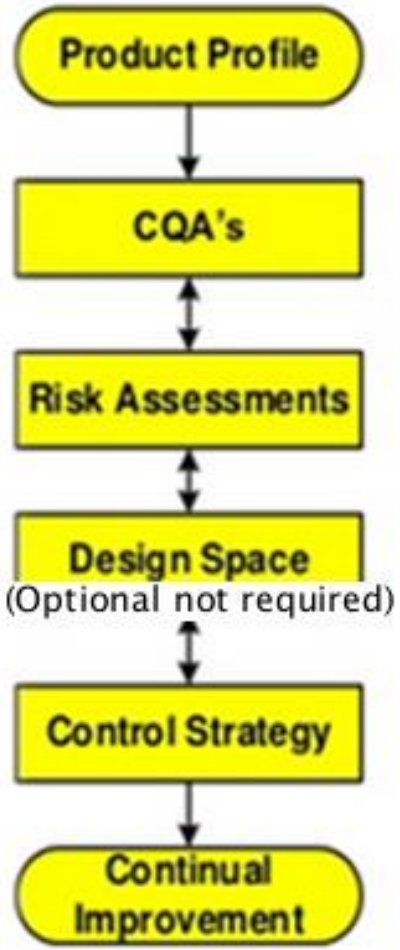
The product lifecycle should facilitate innovation and **continual improvement** and strengthen the link between pharmaceutical development and manufacturing activities, *ICH Q10*

The goals of each product lifecycle stage covers Pharmaceutical Development, Technology Transfer, Commercial Manufacturing and Product Discontinuation.



QbD development steps

- ✓ Begin with a **target product profile** that describes the use, safety and efficacy of the product; define a target product quality profile that will be used by formulators and process engineers as a quantitative surrogate for aspects of clinical safety and efficacy during product development.
- ✓ Gather relevant prior knowledge about the drug substance, potential excipients and process operations into a knowledge space. Use **risk assessment** to prioritize knowledge gaps for further investigation**(CQA and Design Space).**
- ✓ Design a formulation and identify the **critical material (quality) attributes** of the final product that must be controlled to meet the target product quality profile, design a manufacturing process to produce a final product having these critical material attributes.

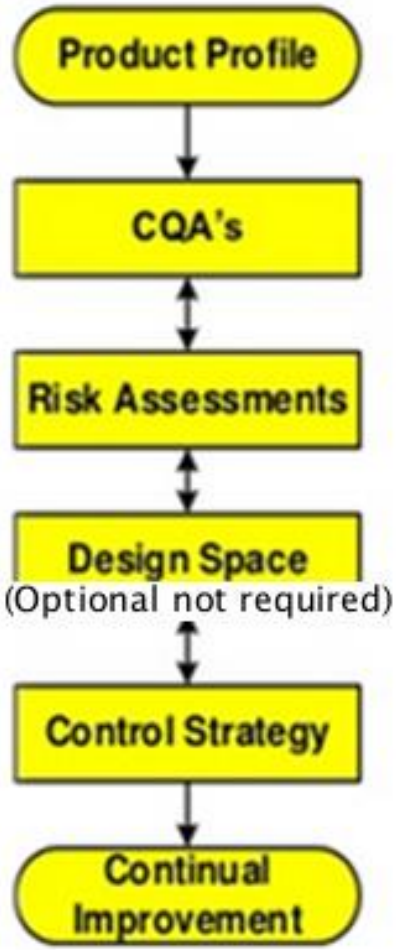


QbD development steps

- ✓ Identify the **critical process parameters** and input (raw) material attributes that must be controlled to achieve these critical material attributes of the final product. Use **risk assessment** to prioritize process parameters and material attributes for experimental verification. Combine prior knowledge with experiments to establish a **design space** or other representation of process understanding.

- ✓ Establish a **control strategy for the entire process** that may include input material controls, process controls and monitors, design spaces around individual or multiple unit operations, and/or final product tests. The control strategy should encompass expected changes in scale and can be guided by a risk assessment.

- ✓ **Continually monitor** and update the process to ensure consistent quality.



Traditional vs QbD approach

Aspect	Minimal Approaches	Enhanced, Quality by Design Approaches
Overall Pharmaceutical Development	• Mainly empirical • Developmental research often conducted one variable at a time	• Systematic, relating mechanistic understanding of material attributes and process parameters to drug product CQAs • Multivariate experiments to understand product and process • Establishment of design space • PAT tools utilised
Manufacturing Process	• Fixed • Validation primarily based on initial full-scale batches • Focus on optimisation and reproducibility	• Adjustable within design space • Lifecycle approach to validation and, ideally, continuous process verification • Focus on control strategy and robustness • Use of statistical process control methods

Traditional vs QbD approach

Aspect	Minimal Approaches	Enhanced, Quality by Design Approaches
Process Controls	• In-process tests primarily for go/no go decisions • Off-line analysis	• PAT tools utilized with appropriate feed forward and feedback controls • Process operations tracked and trended to support continual improvement efforts postapproval
Product Specifications	• Primary means of control • Based on batch data available at time of registration	• Part of the overall quality control strategy • Based on desired product performance with relevant supportive data

Traditional vs QbD approach

Aspect	Minimal Approaches	Enhanced, Quality by Design Approaches
Control Strategy	• Drug product quality controlled primarily by intermediates (inprocess materials) and end product testing	• Drug product quality ensured by risk-based control strategy for well understood product and process • Quality controls shifted upstream, with the possibility of real-time release testing or reduced end-product testing
Lifecycle Management	• Reactive (i.e., problem solving and corrective action)	• Preventive action • Continual improvement facilitated

Quality by Design for Generics

The most prominent challenge identified by Generics manufacturers was a lack of belief in the business case.

However, there are two camps. One half believes that the most important thing for generics is about file first.

The other half believes that today, there is a business case for QbD in generics and is implementing.

When considering all these high level contribution, QbD implementation should be considered also Generics during drug product life cycle management.

QbD-Generic Case study

Step 1: Based on the clinical and pharmacokinetic characteristic of RLD given in the product label as well as the in vitro drug release and physicochemical characteristics of the reference product, a QTPP for the product was defined and justifies.

Attributes	QTPP	Justification
Physical		
Dosage Form	Injection, solution	Similar to RLD
Dosage Strengths	10 mg/0.8ml 7.5 mg/0.6ml 2.5mg/0.5ml 5 mg/0.4ml 1.5mg/0.3ml	Similar to RLD
Fill Volumes	0.3-0.8 ml	Similar to RLD
Volume in container	NLT 0.3ml NLT 0.4ml NLT 0.5ml NLT 0.6ml NLT 0.8ml	Needed for clinical efficacy
Maximum daily dose	10 mg once a day	As per RLD SBOA/PIL/SPC

It is expected that a generic version QTPP should be the same with its reference product.

QbD-Generic Case study

Attributes	QTPP	Justification
Physical		
Description	Clear and colorless to slightly yellow	Similar to RLD
Completeness and clarify of solution	Meets the requirement of current USP General Chapter <1>	Needed for safety and efficacy
Particulate matter	Meets the requirement of current USP General Chapter <788> Not more than 6000 average number of particles should be grater than or equal to 10 µm Not more than 600 average number of particles should be grater than or equal to 25 µm	Needed for safety
Stability	Stability studies should be conducted for 24 months at 25°C/60%RH, 12 months at 30°C/65%RH, 6 months at 40°C/75%RH,	For regulatory filling and determining shelf life
pH	5-8	Needed for stability

QbD-Generic Case study

<table>
<tr><th>Attributes</th><th>QTPP</th><th>Justification</th></tr>
<tr><td colspan="3">Chemical</td></tr>
<tr><td>Assay</td><td>12.5 mg/mL
12.5 mg/mL
5 mg/mL
12.5 mg/mL
5 mg/mL</td><td>Needed for efficacy</td></tr>
<tr><td>Residual solvent content</td><td>As per ICH</td><td>Needed for safety</td></tr>
<tr><td>Releated substances</td><td><table><tr><th>Release</th><th>Shelf-life</th></tr><tr><td>Imp-A NMT 0.25%
Imp-B NMT 0.25%
Max. Unknown imp NMT 0.20%
Total Imp. NMT 2.0%</td><td>Imp-A NMT 0.40%
Imp-B NMT 0.40%
Max. Unknown imp NMT 0.20%
Total Imp. NMT 3.0%</td></tr></table></td><td>Needed for safety</td></tr>
</table>

QbD-Generic Case study

Attributes	QTPP	Justification
Biological		
Intended use	Prevention of VTE	Needed to be similar to RLD
Route of administration	Subcutaneous	Needed to be similar to RLD
Microbiological		
Sterility	The sample should pass the sterility test(meet the requirement of current USP General Chapter<71>).	Needed for safety
Bacterial Endotoxin	NMT 2.2 EU per mg of API(Meet the requirements of current USP General Chapter<85>).	Needed for safety

QbD-Generic Case study

Attributes	QTPP	Justification
Packaging and Storage Details		
Container Closure System	Single-dose, vial	Needed for primary pack integrity
Storage Condition	Store at 25°C room temperature.	Needed for stabiliity and safety
Label Claim	Each vial contains 1.5/2.5/5/7.5/10 mg API and sodium chloride	Needed to be similar to RLD

QbD-Generic Case study

Step 2: CQAs are defined based on the severity of harm of QA to product safety and/or efficacy with using risk assesment, should be evaluated during formulation development studies.

Attributes	QTPP	Whether it is CQA or not?	Justification
In-process (Bulk solution)			
Description	Clear and colorless to slightly yellow	Yes	Description of drug product is a direct indication for any physicochemical change in drug product. Hence it is regarded as critical attribute. It will be mainly controlled through material spesification and manufacturing process.
Identification by HPLC	The RT of the major peak in the chromatogram of the test preparation corresponds to that of the standart preparation as obtained in te assay.	No	Test is kept to confirm the presence of API in formulation. PAI spesification(identification) will be the control for identification of finished product. Not a CQA. So It is not a critical attribute.

How much does each CQA affect each QTPP?

QbD-Generic Case study

Attributes	QTPP	Whether it is CQA or not?	Justification
In-process (Bulk solution)			
Assay by HPLC	Not less than 98.0% and not more than 102.0% of labelled amount of API.	Yes	Low or high assay willl impact the assay of the final drug product which in turn will impact the safety and efficacy profile. Hence, it is regarded as critical attribute.
pH of solution	5-8	Yes	pH of solution is regulated with amount of acide in formulation and has an impact on the drug product stability. Hence, it is regarded as critical attribute.

QbD-Generic Case study

Attributes	QTPP	Whether it is CQA or not?	Justification
In-process (Bulk solution)			
Bioburden	NMT 10 CFU/ 100 ml	Yes	Has direct impact on sterility assurance level in finished product and in turn on patient safety. Hence, it is regarded as critical attribute.
LAL testing	NMT 2.2 EU per mg of API	Yes	Presence of LAL has direct impact on the safety of the patient. It will be controlled through API and excipients spesification. Hence, it is regarded as critical attribute.

QbD-Generic Case study

Attributes	QTPP	Whether it is CQA or not?	Justification
Finished Product			
Description	Clear and colorless to slightly yellow	Yes	Description of drug product is a direct indication for amy physicochemicalchange in drug product. Hence, it is regarded as critical attribute.
Completeness and clarify of solution	Meets the requirement of current USP General Chapter <1>	No	sodium chloride has a good miscibility, so it is not a critical attribute.
pH of solution	5-8	Yes	pH of solution is regulated with amount of acide in formulation and has an impact on the drug product stability. Hence, it is regarded as critical attribute.
Assay by HPLC	Not less than 98.0% and not more than 102.0% of labelled amount of API.	Yes	Low or high assay willl impact the assay of the final drug product which in turn will impact the safety and efficacy profile. Hence, it is regarded as critical attribute.

QbD-Generic Case study

Attributes	QTPP	Whether it is CQA or not?	Justification
Finished Product			
Releated substances	<table><tr><th>Release</th><th>Shelf-life</th></tr><tr><td>Imp-A NMT 0.25% Imp-B NMT 0.25% Max. Unknown imp NMT 0.20% Total Imp. NMT 2.0%</td><td>Imp-A NMT 0.40% Imp-B NMT 0.40% Max. Unknown imp NMT 0.20% Total Imp. NMT 3.0%</td></tr></table>	Yes	Impurities in finished product will have direct impact on the patient's safety. Initial levels of impurities are controlled trough input API spesification and manufacturing under GMP condition to avoid contamination issue . Formulation will be designed taking into accont the degredation profile of API. Levels of impuritied in dry product will be kept as per ICH guidelines. Hence, it is regarded as critical attribute.

QbD-Generic Case study

Attributes	QTPP	Whether it is CQA or not?	Justification
Finished Product			
Particulate matter	Meets the requirement of current USP General Chapter <788> Not more than 6000 average number of particles should be grater than or equal to 10 µm Not more than 600 average number of particles should be grater than or equal to 25 µm	Yes	It should be devoid of any particulate contamination. Double filtration and GMP area for complete manufacturing control particulate matter in finished product. Hence, it is rearded as critical attribute.
Sterility	The sample should pass the sterility test(meet the requirement of current USP General Chapter<71>).	Yes	Parenteral product should be sterile. Double filtration and aseptic processing ensures sterile product. Hence, it is rearded as critical attribute.

QbD-Generic Case study

Attributes	QTPP	Whether it is CQA or not?	Justification
Finished Product			
Bacterial Endotoxin	NMT 2.2 EU per mg of API(Meet the requirements of current USP General Chapter<85>).	Yes	Presence of BET has direct impact on the safety of the patient. GMP area for complete manufacturing treatment of primary packaging material and low BET grade of raw material are used to control BET in finished prıduct. Hence, it is rearded as critical attribute.
LAL testing	NMT 2.2 EU per mg of API	Yes	Presence of LAL has direct impact on the safety of the patient. It will be controlled through API and excipients spesification. Hence, it is regarded as critical attribute.
Residual solvent	As per ICH	No	Controlled through input material and designed process in finished product below acceptable limits. So, it is not a critical attribute.

QbD-Generic Case study

Step 3: CPPs are defined for every process steps.

Process step	Process Parameter
Mixing	Capacity of Unit
	Fill volume
	Temperature of liquid and time
	Mixing time
	Mixing speed
Filtration	Filter type and size
	Filtration speed
	Filtration time
	Pump type
Filling&Sealing	Filling speed
	Filling time
	Pump type

How much do Process Parameter affect the Quality Attributes?

QbD-Generic Case study

A risk assessment of overall drug product manufacturing process was performed to identify the high risk steps could affect the final drug product CQAs.

Unit Operation Parameters	Product CQA									
	Description	pH	Assay	RS	Volume in Container	Water content	Particulate matter	BET	Bioburden	Sterility
Dispensing										
Dispensing	NI	Low	Low	NI	NI	NI	NI	NI	NI	NI
Compounding										
Time duration	Medium	Low	Medium	Low	NI	NI	NI	NI	NI	NI
Temperature of solution	Low	NI	Medium	Medium	NI	Low	NI	NI	NI	NI
Mixing RPM	Low	Low	Medium	NI	NI	NI	NI	NI	NI	NI
Occupancy	NI	NI	Low	NI	NI	NI	NI	NI	NI	NI
Nitrogen Pressure	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Filtration (Offline and Online)										
Integrity of filter	NI	NI	NI	NI	NI	NI	Medium	NI	Medium	High
Filtration time	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Filtration Pressure	NI	NI	NI	NI	NI	NI	Medium	NI	Medium	High
Filling										
Filling speed	NI	NI	NI	NI	High	NI	NI	NI	NI	NI
Filling time	NI	NI	NI	Medium	NI	NI	NI	NI	NI	High
Pre and Post Nitrogen flushing	NI	NI	NI	Medium	NI	NI	NI	NI	NI	NI
Stoppering										
Stoppering Speed	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Sealing										
Sealing speed	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Seal Integrity	NI	NI	NI	NI	NI	NI	NI	NI	NI	High
Packaging										
Environmental Conditions (Normal Light and Room Temperature)	NI	NI	NI	Low	NI	NI	NI	NI	NI	NI
Aseptic Processing										
Aseptic Processing	NI	NI	NI	NI	NI	NI	Low	Low	Medium	High

Based on the preliminary risk assessment it was concluded that unit operations like compounding, filtration, filling and stoppering sealing have agreed medium/high risk to drug product.

QbD-Generic Case study

Step 4: CMAs are defined for every excipient and APIs.

S. No	Excipient Characteristics	Product CQA's										Unit operations-CPP's						Packaging
		Description	pH of solution	Assay	Related Substances	Volume in Container	Water content	Particulate matter	BET	Bioburden	Sterility	Dispensing	Compounding	Filtration	Filling	stoppering	Sealing	
1	Description	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
2	Solubility	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	Medium	NI	NI	NI	NI	NI
3	Identification	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
4	Clarity of solution	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
5	Color of solution	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
6	Sulfates	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
7	Heavy Metals	NI	NI	NI	Medium	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
8	Water by KF	NI	NI	NI	NI	NI	Medium	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
9	Residue on Ignition	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
10	Oxalic Acid	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
11	Readily carbonisable substance	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
12	Bacterial Endotoxins	NI	NI	NI	NI	NI	NI	NI	Medium	NI	NI	NI	NI	NI	NI	NI	NI	NI
13	Assay	NI	Medium	NI	High	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI

How much do Material Attributes affect the Quality Attributes and Process Parameters?

QbD-Generic Case study

Critical Quality Attributes		Critical Process Parameters	Critical Material Attributes	
Bulk solution	**Finished Products**	Mixing time	**Excipient**	**API**
Description	Assay by HPLC	Mixing speed	Solubility	Description
Assay by HPLC	pH of solution	Temperature of liquid and time	Heavy metals	Solubility
pH of solution	Particulate matter	Filtration speed	Water by KF	Water content
Bioburden	Related substances	Filter type and size	Bacterial Endotoxins	Heavy metals
LAL testing	Bioburden	Filtration time	Assay	Releated substance
	LAL testing			Bacterial endotoxins
	Sterility			Microbial limit testing

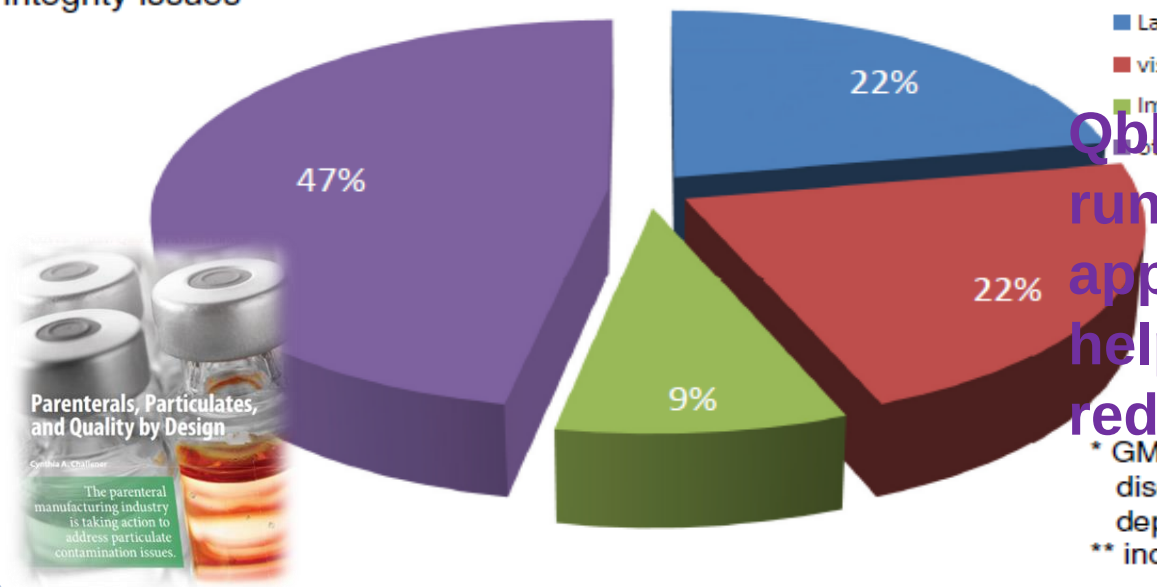
Investigation would be done during development step in order to reduce the risk.

Conclusion…

190 million liters of intravenous fluids are administered to patients each year in the United States. Several different clinical effects ranging from minor problems to serious complications and death have occurred as a result of the injection of **particulate matter***.

FDA sterile injectable drug recalls 2008-2012

In the past years, the regulator has paid increasingly more attention to container closure integrity issues



QbD may be long run but use of a QbD approach should help the industry reduce costs.

* GMP failures, crystallization, discoloration all product dependent

** includes CCI defect

**Parenterals, Particulates, and Quality by Design, Pharmaceutical Technology Volume 38, Issue 11 Nov 02, 2014*

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